REVIEW

Synthesis and Biomedical Applications of Polymer-Functionalized Magnetic Nanoparticles

Article history:
Received: 21-05-2023
Revised: 10-08-2023
Accepted: 23-08-2023

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Abstract: Magnetic nanoparticles (MNPs) are receiving increasing attention from individual scientists and research companies as promising materials for biomedical applications. MNPs can be synthesized by many different methods. Before proceeding to the synthesis process, the cost of using it and the practicality of the synthesis conditions are well investigated. Especially in their use in the biomedical field, features such as not containing toxic substances, high biocompatibility, and low particle size are desired. However, the use of magnetic nanoparticles in biomedical applications is limited due to various difficulties such as particle agglomeration and oxidation of magnetic cores of MNPs. To overcome these challenges, MNPs can be coated with various natural and synthetic polymers to alter their morphological structure, magnetic character, biocompatibility, and especially surface functional groups. Therefore, this review focuses on the synthesis of MNPs by different methods and the effects of these synthesis methods on magnetic properties and size, their modifications with natural and synthetic polymers, and the use of these polymer-coated MNPs in biomedical fields such as targeted drug release, enzyme immobilization, biosensors, tissue engineering, magnetic imaging, and hyperthermia. The review article also provides examples of advanced biomedical applications of polymer-coated MNPs and perspectives for future research to promote polymer-coated MNPs. To this end, we aim to highlight knowledge gaps that can guide future research to improve the performance of MNPs for different applications.

Keywords: Magnetic nanoparticles; natural and synthetic polymers; surface modifications; biomedical applications.

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1. INTRODUCTION

Materials between 1 and 100 nm in size have been called nanomaterials. Nanomaterials can be found in various formulations, such as nanoflowers, nanofibers, dendrimers, and nanoparticles (NPs) (Hedayatnasab *et al.*, 2017). Among these materials, NPs are of great interest due to the practicality of synthesis and application and the wide range of uses (Sakallıoğlu, 2013). Depending on the purpose of use, various synthesis methods can obtain NPs of the desired size and properties. For instance, NPs thought to be applied in biomedical fields should be compatible with body conditions, not show toxic effects, ease of passage through areas such as the blood-brain barrier, and should not obstruct the vessels. While performing such a nanoparticle synthesis, it is necessary to choose one method that contains as little content as possible in terms of the practicality of the synthesis method, ease of production, and toxic substances (Tran& Webster, 2010). However, while

the synthesis method is preferred, it is expected to be affordable in terms of cost and features. Considering this information, it is thought that MNPs from the NPs class provide a high potential for biomedical applications. It is well known that MNPs can be synthesized in different compositions including iron oxides, gamma-Fe_2O_3, powdered metals, spinel ferrimagnets, and alloys. The synthesis methods of MNPs such as green synthesis, co-precipitation, and hydrothermal methods are highly preferred because of their advantages (Ajinkya *et al.*, 2020).

MNPs, which can be synthesized from nano to micron sizes, are a highly preferred nanomaterials for biomedical applications due to their high biocompatibility, low toxicity, simple synthesis procedures, and affordability. Also, they can be steered via external magnetic fields. The biomedical applications of MNPs can be listed as drug release, enzyme immobilization, magnetic resonance imaging (MRI), and biosensor applications. But their structure, magnetic nanoparticles tend to collect and collapse after a while. This may cause intravascular accumulation or tissue accumulation, especially in drug applications. In addition, it is not easy for them to pass through selective systems such as the blood-brain barrier. Therefore, modifying the surface of the magnetic nanoparticle with a polymer selected for the application area provides lower toxicity for *in vivo* studies. In addition, since it will search for resolutions, the tendency to aggregate and collapse is reduced. It is wrong to say that MNPs are preferred in biomedical fields because they are only biocompatible (Markides *et al.*, 2012). Suppose, in enzyme immobilization. In that case, enzymes may lose some of their activities during the immobilization process. To avoid this disadvantage, enzymes can be immobilized to a magnetic carrier matrix, and the activity can be increased with the support of an external magnetic field. In addition, when drug release is examined, it is known that both MNPs and other nanoparticle formulations tend to collect and collapse in the vein after a while. While no interference can be made to other nanoparticle classes in drug release studies, MNPs are triggered from outside the body with the help of an external magnetic field, preventing their accumulation in the vein and, if desired, controlled release by making an on-off feature for drug release. In addition to all these advantages, the accumulation and collapse of MNPs due to their structure is known as the main disadvantage. For these reasons, the outer layer of MNPs is coated with a suitable polymer (Reddy *et al.*, 2012).

The polymer coating process reduces the coagulation properties of MNPs and provides various functional properties. Appropriate polymer classes for modification are given in Table 1. Increasing the biocompatibility, preventing the precipitation of MNPs and enabling them to dissolve easily can be cited as why natural polymers are preferred among polymer classes for biomedical applications (Sakallıoğlu H., 2013). There are main factors to consider when choosing which polymer to use for coating the nanoparticle. It is necessary to determine in advance what the nanoparticle will be used for and to make the design. For example, while a biocompatible polymer is preferred for *in vivo* studies, the nanoparticle surface can also be coated with a synthetic polymer for studies such as dye removal. When polymers are examined in general, as mentioned before, they stand out as safe materials in *in vitro* and *in vivo* tests due to their high biocompatibility. *In vitro* studies have confirmed that it does not show cytotoxic or genotoxic properties unless high concentrations are increased. In studies applied to experiment animals, studies are reporting that polymer functional materials cause toxic effects when used in very high doses and given parenterally. When the pathological evaluations are considered in general, no effects that may cause disorders in organ and cell levels have been observed (Ritter *et al.*, 2020). If we give examples of different surface coating methods here, Yang *et al.*, in their study, preferred surface-initiated atom transfer radical polymerization (ATRP) and grafting method for coating magnetic nanoparticles with poly(N-isopropylacrylamide) (PNIPAM). This grafting method is generally defined as surface-initiated polymerization. In this method, the basic approach is initiating the polymer chain from the surface by immobilization of a monolayer of surface initiators followed by *in situ* polymerization of the selected monomers, while the logic of grafting is the direct application of the polymer-functional surface.

Then, magnetic@PNIPAM nanoparticles coated with this method were used in drug release applications. Another study, Keng *et al.*, reported a practical synthesis of CoNp synthesized from the thermolysis of $Co_2(CO)_8$) with polystyrene surfactants prepared using the ATRP method. The solutions of the nanoparticles obtained by this method, which were poured on the supporting substrates, were also investigated. Here, a tendency for adjacent chains to form a zippered configuration was observed in addition to the local nematic-like arrangement of the

nanoparticle chains. In this comprehensive review, the synthesis methods and biomedical applications of polymer-coated MNPs were examined, and their advantages over other nanoparticle classes were presented. One of the main features distinguishing this compilation from other compilations is that it was created by following the studies carried out closer to the present day. We anticipate that this review will inspire future exploration of polymer-coated MNPs, focusing on the needs of targeted applications.

Magnetic Core-Polymer	Biomedical Application	Reference
Fe_3O_4-Chitosan	Drug Delivery	(Manjusha *et al.,* 2023; Yusefi *et al.,* 2023; Liu *et al.,* 2023; Ding *et al.,* 2015; Karthika *et al.,* 2020; Adimoolam *et al.,* 2018)
	MRI Imaging	(Wang *et al.,* 2021; Song *et al.,* 2015; Zhao *et al.,* 2014; Imran *et al.,* 2023)
	Biosensor	(Tiama *et al.,* 2023; Zhou *et al.,* 2018; Chaichi and Ehsani, 2016)
	Hyperthermia	(Qu *et al.,* 2010; Mai *et al.,* 2012)
Ni-O Poly (3-hydroxybutyrate)/poly(amine)	Drug Delivery	(Salahuddin *et al.,* 2020)
$NiFe_2O_4$- PEG	Hyperthermia	(Shabani *et al.,* 2023)
Ni-O-polydopamine	Drug Delivery	(Binu *et al.,* 2021)
Fe_3O_4-PVA	Drug Delivery	(Moghaddam-manesh *et al.,* 2022)
$NiFe_2O_4$-Polyacrylic Acid	MRI imaging	(Irfan *et al.,* 2021)
Co_3O_4-Polyaniline	Antifungal Agents	(Manzoor *et al.,* 2021)
Fe_3O_4-PEG	Drug Delivery	(Karimi and Namazi, 2021; Ebadi *et al.,* 2023)
	MRI imaging	(Chen *et al.,* 2015)
	Biosensor	(Antarnusa *et al.,* 2022)
	Enzyme Immobilization	(Li *et al.,* 2022; Kharazmi *et al.,* 2020)
Fe_3O_4-PVA	Enzyme Immobilization	(Laleh *et al.,* 2020; Liu *et al.,* 2020)
	Drug Delivery	(Taheri-Ledari *et al.,* 2020; Zandi *et al.,* 2022)
	MRI Imaging	

Table 1. Some commonly used polymers for nanoparticle functionalization and their applications.

2. THE SYNTHESIS METHODS OF MNPs

The expansion of the applications of MNPs in biomedical fields has brought with it the interest in synthesis methods Where and how MNPs will be used depends on their structural, magnetic, and morphological properties. For this reason, synthesis methods should be known in detail to obtain MNPs with the desired design for application areas. There are various procedures for the synthesis methods of MNPs. In this section, the most commonly preferred synthesis procedures for the use of MNPs in the biomedical field were discussed.

2.1. Green synthesis

Green synthesis is one of the most preferred methods among MNPs synthesis methods. This is because lower levels of toxic chemicals are used during the synthesis of NPs obtained by this method compared to other methods. The main advantages of this synthesis are that it is environmentally friendly and consists of safe components that do not show toxic properties. In addition, in this synthesis method, NPs are obtained using any biological material (Majidi *et al*., 2016). For example, in magnetic nanoparticle preparation, fungi (Vigneshwaran

et al., 2007), plants (Chandran *et al.*, 2006; Song & Kim, 2009), enzymes (Willner *et al.*, 2006), and microorganisms (Klaus *et al.*, 1999; Nair & Pradeep, 2002; Abbasi *et al.*, 2014) are known to be used. It was observed that plants and plant extracts were preferred more than others in these samples. This is because plants contain biomolecules such as flavonoids, reductases, ascorbic acid, citric acid, and dehydrogenase (Pandey *et al.*, 2012). The visual figure of this method is presented in Fig. 1. In summary, the green synthesis method has advantages such as being economical, environmentally friendly, and non-toxic. In addition, the use of biological molecules in the synthesis stage makes this method especially attractive for biomedical applications (Yang & Yan, 2012).

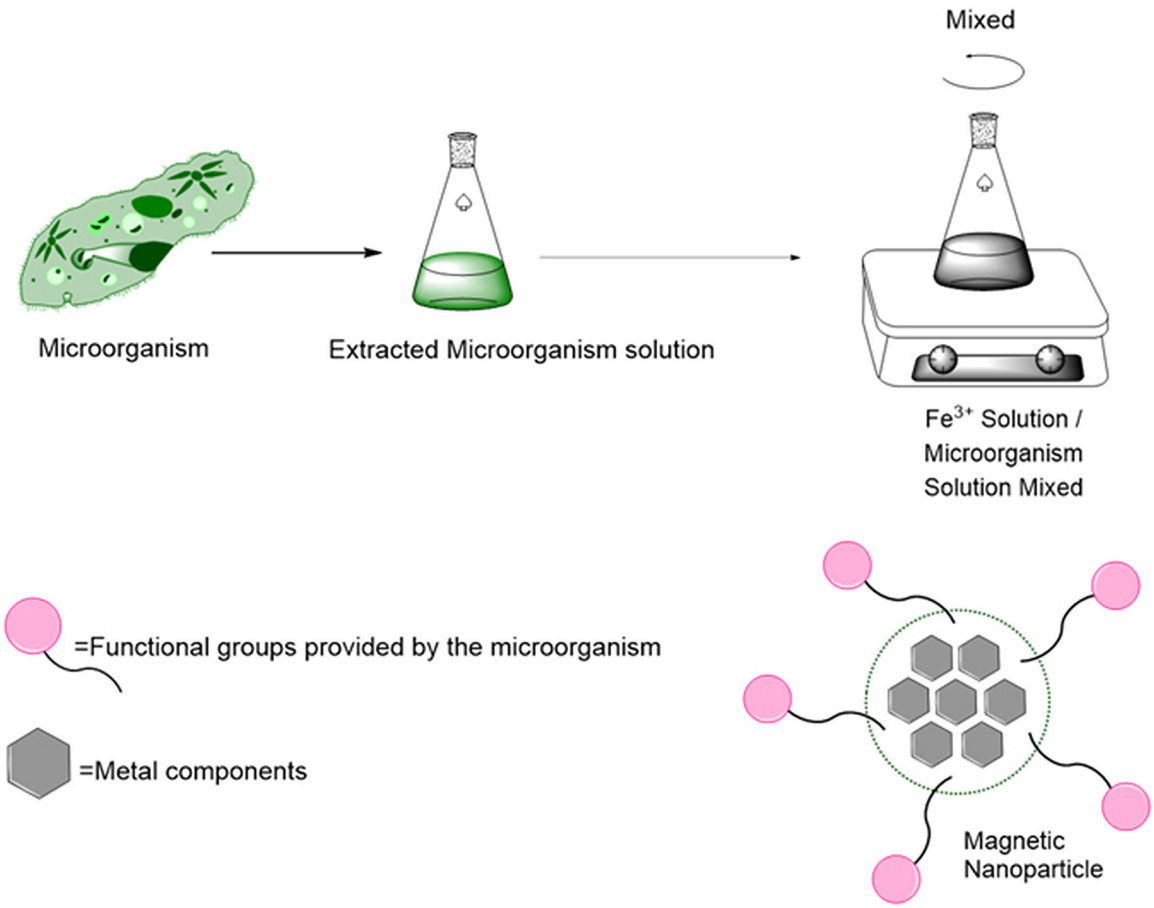

Figure 1. Schematic representation of MNPs obtained by the green synthesis method (Singh *et al.*, 2020).

2.2. Co-precipitation

The co-precipitation method is one of the most preferred methods among MNPs synthesis methods. The main advantage of this method is its high ease of application and low toxic substance content to synthesize MNPs in controlled sizes. When the studies on MNPs are examined in the literature, MNPs obtained by the co-precipitation method are frequently encountered. The reason why it is so intensely preferred is not only the factors mentioned above. The simplicity of the synthesis method and its low cost have led to an increased interest of researchers in this method. The most common type of MNPs this method is usually iron oxides. Iron oxides are obtained by mixing iron or iron ions at high temperatures with the addition of a 1:2 ratio (Sandeep Kumar, 2013; Wu *et al.*, 2015). The visual of the co-precipitation method is shown in Fig. 2. The reaction conditions are highly effective on the structural and morphological properties of the iron oxides obtained by this method. It has been previously

reported in the literature that the conditions that may affect these properties are the pH value of the environment and ions such as chlorides, sulfates, nitrates, and perchlorates in the environment (Wu *et al.*, 2008). Therefore, great care should be taken to create suitable reaction conditions during synthesis. Although the MNPs obtained by the co-precipitation method have a more specific surface area and surface energy due to the minimal particle size, their high magnetizability and low toxic substance content make this method suitable for biomedical applications.

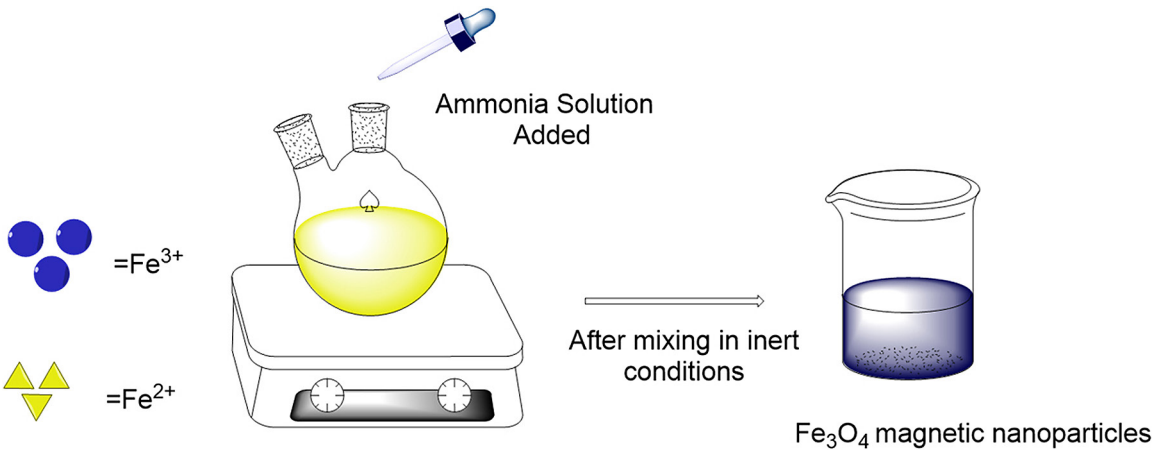

Figure 2. Schematic diagram of the co-precipitation method (Chaudhary and Chaudhary, 2018).

2.3. Microemulsion

In the microemulsion synthesis method, a surfactant in the reaction medium is needed to obtain NPs. In this synthesis method, MNPs are obtained by thermodynamically stable dispersion of water and oil phases that do not mix in the presence of surfactant (Majidi *et al.*, 2016). Some important points make the microemulsion method advantageous compared to other methods. These can be listed as simple equipment, control of particle size, high magnetizability, and significant control over the design of the MNPs to be synthesized. In addition, it is a very convenient method for obtaining MNPs with high crystalline properties (Wu *et al.*, 2008; Chin& Yaacob, 2007). When the microemulsion synthesis method is planned, the surfactant should be carefully preferred. The reason for this is that the structural and morphological properties of the molecules to be obtained using this method depend on the structure of the surfactant (Sánchez *et al.*, 2014). Preferred surfactants are amphiphilic molecules that lower the interfacial tension (Faraji *et al.*, 2010). The choice of surfactant for the synthesis process depends on the reaction system's physicochemical properties. In summary, microemulsion method shows a high potential for synthesizing MNPs with high magnet values in controlled size.

2.4. Hydrothermal synthesis

This method is also known as the solvothermal method. This method is highly advantageous for synthesizing MNPs. High temperature and pressure are used while performing the synthesis with this method. The most important distinguishing factor of this method from the thermal decomposition method is the use of pressure during the reaction (Butter *et al.*, 2005). This method's method is schematized in Fig. 3. It is thought that there are two important reasons why this method is preferred compared to other methods. The first is obtaining a uniform crystal structure, and the second is the controllability of nanoparticle morphology during synthesis (Li *et al.*, 2013; Li *et al.*, 2014). When the literature on MNPs synthesized by hydrothermal method is examined, it has been observed that these NPs have been developed especially in MRI applications and exhibit high potential in other applications (Lai *et al.*, 2012).

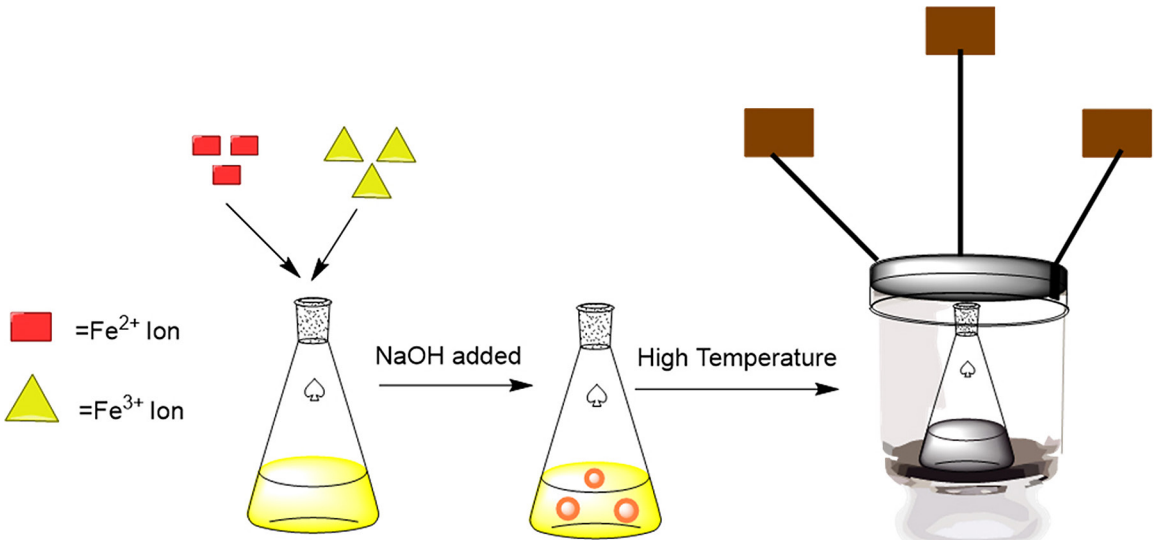

Figure 3. Hydrothermal synthesis scheme of MNPs (Yadav *et al.*, 2020).

2.5. Thermal decomposition

Synthesis reactions during the production of MNPs are usually carried out at room conditions. The thermal decomposition method uses high temperatures during the reaction instead of these traditional conditions (Sun & Zeng 2002; Li *et al.*, 2008). Herein, MNPs are obtained by dissolving magnetic metal ions at high temperatures in the presence of organic surfactants. It can also be said that after the organometallic composites are decomposed using high temperatures, oxidation in organic solvents is provided by using stabilized surfactants with levers under these conditions. It is known that NPs synthesized by this method provide good size control and have high crystalline properties. The visual schema of this method is shown in Fig. 4. It is known that the most widely used biomedical application of MNPs synthesized by this method is MRI contrast material.

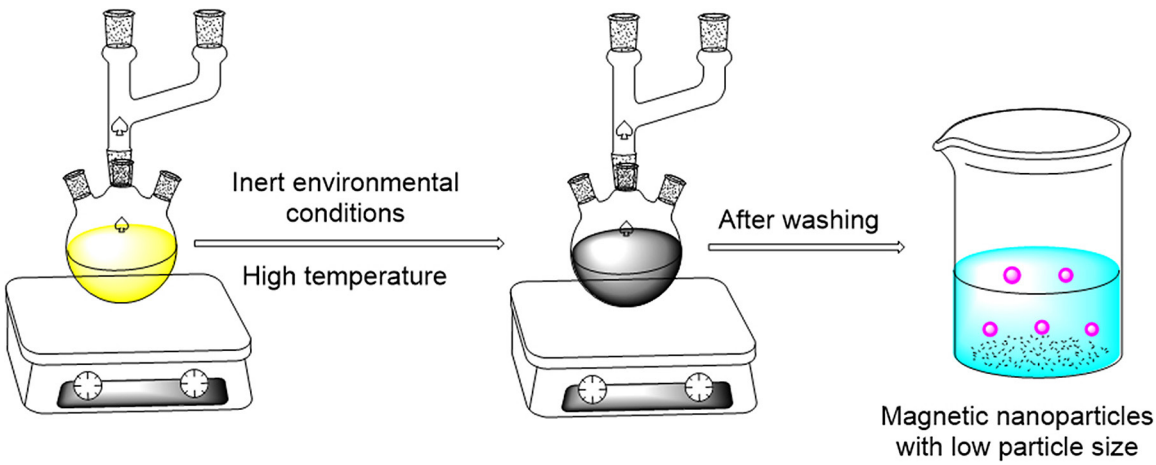

Figure 4. Schematic of synthesis of MNPs by thermal decomposition method (Chaudhary and Chaudhary, 2018).

2.6. Ultrasonic synthesis

The sonochemical method for synthesizing MNPs is based on using high-intensity ultrasonic irradiation by taking advantage of the chemical effects caused by acoustic cavitation to form these nanoparticles (Jain *et al.*, 2005). Ultrasonic sound waves create bubbles that undergo compression and expansion, which causes the bubbles to be released. These bubbles accumulate by storing ultrasonic energy until they collapse. When the collapse of the bubbles is complete, a localized burst of energy occurs, which is short-lived and increases the pressure at a high rate. This method is an extremely advantageous for obtaining MNPs dispersed in graphite oxides and composite molecules such as latex beads (Veiseh *et al.*, 2010). This method makes it possible to obtain MNPs with low crystallinity but with high magnetic saturation and in controlled sizes (Corot *et al.*, 2006). The visual of this method is shown in Fig. 5.

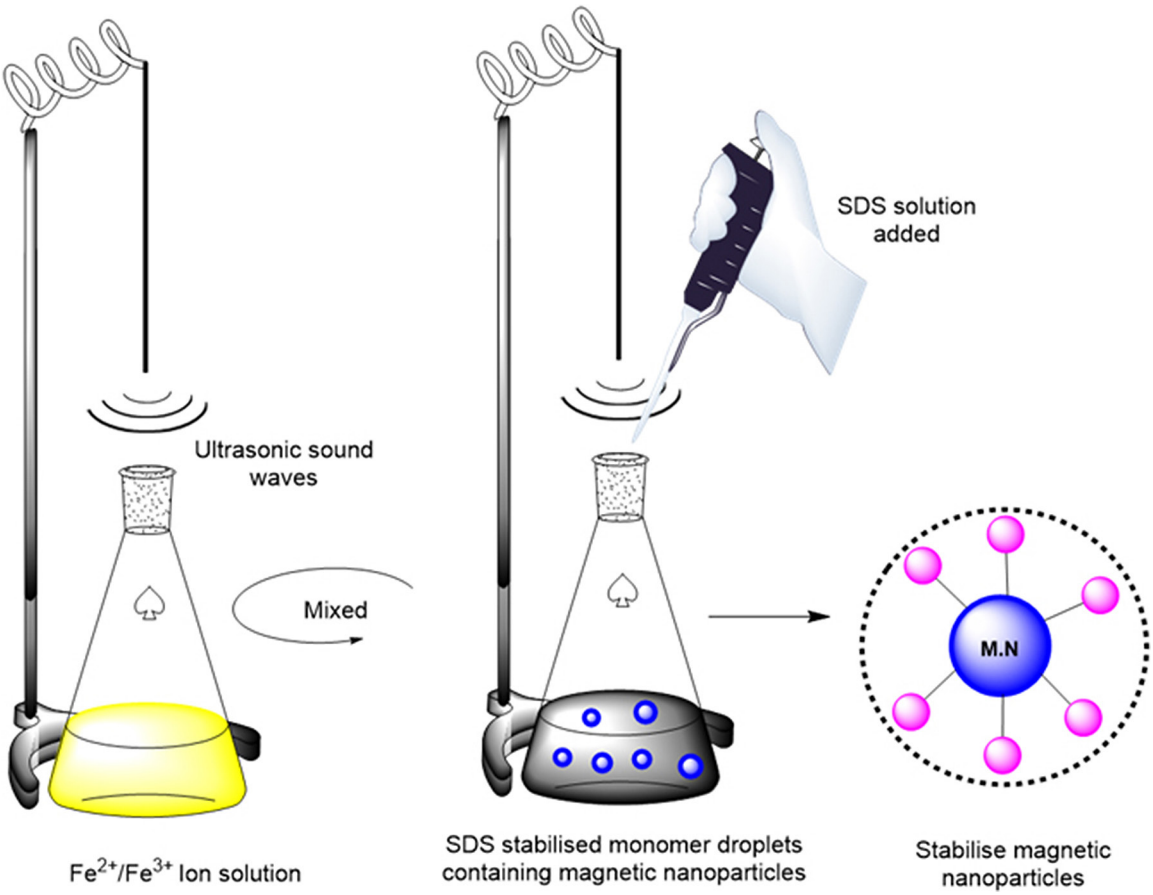

Figure 5. Schematic representation of MNPs synthesis by ultrasonic method (Dheyab *et al.*, 2021).

3. BIOMEDICAL APPLICATIONS OF POLYMER-COATED MNPs

3.1. Drug delivery

Research on combating diseases and providing effective treatments has been ongoing for many years. It is known that drugs and drug delivery systems developed from the past to the present are used to treat infectious diseases and damaged tissues. These drugs and drug delivery systems can be developed in synthetic and natural formulations. However, the spread of different types of diseases day by day or the restrictions in the applications of drugs used in existing diseases have increased research in this field. While developing new-generation drugs and drug delivery systems, attention is paid to features such as good distribution even

in narrow areas and crystal morphology. In addition, the synthesis and release of targeted drug delivery systems is very important for developing different carrier matrices (Dobson, 2006; Lombardo *et al.*, 2019). MNPs are at the forefront of structures that have an important potential in the field of drug targeting. MNPs are directed from the outside with the help of an external magnetic field to provide great convenience in directing the drug to the target region. In addition, while the ability to synthesize MNPs in desired sizes is effective on drug loading efficiency and release rate, MNPs, especially synthesized in small sizes, can be easily used in intravenous applications without causing obstruction. However, the surface of MNPs can be modified with a suitable polymer. This modification allows magnetic carrier systems to pass through the blood-brain barrier easily. In addition, properties such as thermo-sensitivity can be added to their structures depending on the type of polymer. In this section, drug delivery applications of MNPs will be emphasized, and their effectiveness will be discussed (Sayıner & Çomoğlu, 2016).

Yu *et al.* synthesized MNPs by coaxial electrospraying method and loaded paclitaxel (PCX). The stages of this experiment are schematized in Fig. 6. Advantageous aspects of nanoparticles are so important that they cannot be ignored in drug release studies. Herein, besides the physicochemical characterization of the synthesized MNPs, the effects of drug release on the A549 cell line were also investigated. While creating a magnetic core within the scope of the study, the outer shell was also coated with poly(lactic-co-glycolic acid), a biocompatible polymer, by electrospraying. According to the findings obtained from the experimental data, it was determined that the synthesized MNPs had a suitable morphological structure, high drug encapsulation and long-term release. Findings obtained from *in vivo* studies showed that the synthesized MNPs were more effective than cold atmospheric plasma (CAP) treatment applied alone compared to similar studies in the literature. This study has significant potential for developing integrated use of drug-loaded MNPs and cold plasma therapy in many cancer types (Yu *et al.*, 2018).

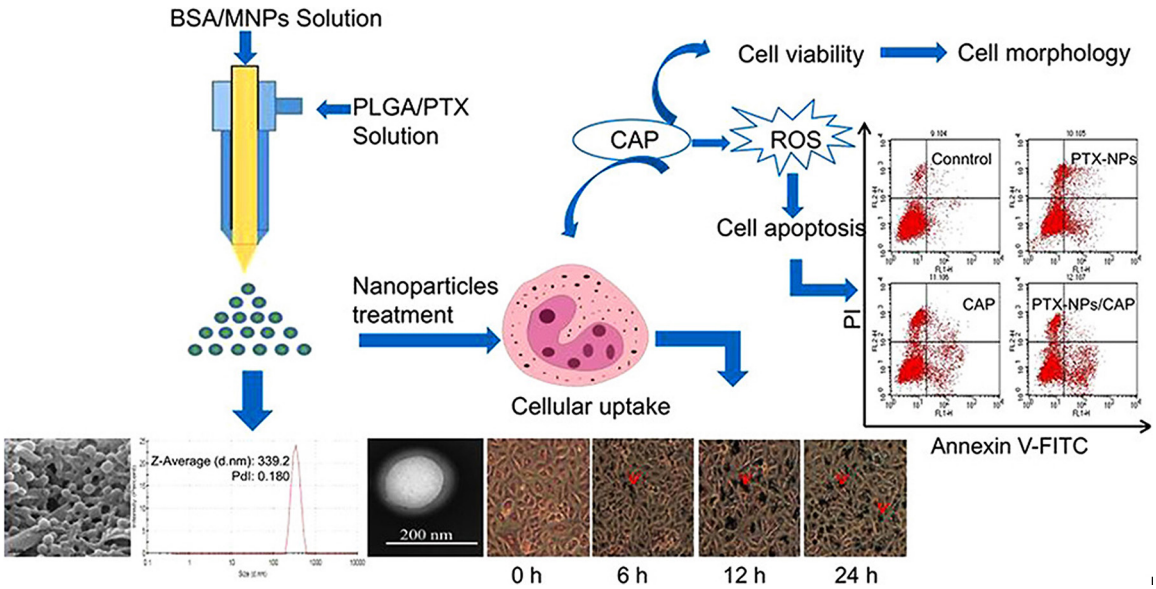

Figure 6. Schematic of the synthesis of paclitaxel-loaded magnetic nanoparticles (Yu *et al.*, 2018).

Yin *et al.* synthesized MNPs consisting of $ZnFe_2O_4$ core and modified with silica shell with mesopores (Yin *et al.*, 2018). Thanks to these synthesized magnetic-shell nanoparticles, simultaneous drug release was achieved, and the chemo-resistance of drugs used to treat breast cancer was overcome. The drugs used as examples in this study are letrozole (let-7a) and doxorubicin (Dox). While the silica shell in the structure is involved in loading Dox, it also binds with let-7a through secondary interactions. The findings obtained from this study showed that the tumor volume of the applied method decreased over 90% *in vivo* and 85% *in vivo*. The findings show that this developed method

is more advantageous than traditional methods. In summary, within the scope of this study, magnetic core-polymer shell NPs were successfully synthesized and simultaneous drug release was achieved. This study is very important for the development of synergistic drug release studies.

Guisasola *et al.* synthesized magnetic mesoporous silica NPs for drug release (Guisasola *et al.*, 2018). Firstly, super-paramagnetic iron oxides were synthesized and covered with a silica matrix. Silica has a significant impact on the exterior drug loading capacity. The external layers of MNPs with silica surface as the last step of the synthesis stage are covered with a heat-sensitive polymer. A schematic illustration for this study is shown in Fig. 7. The reason for the preference of a heat-sensitive polymer can be considered as the formation of gaps on the surface of the nanoparticles that allow the drug to access cancerous tissues. Within the scope of the study, an external magnetic field of triggering drug release was applied. The presence of magnetic fields has a synergistic effect between chemotherapy and hypertmia, causing both heating and alternative magnetic field movement on MNPs. According to the findings obtained from the experiments, this emission has significantly inhibited tumor cell growth after 48 h. In addition, this study observed that this treatment could be performed effectively with a smaller magnetic loading, not with large amounts of magnetic loading, as in other hyperthermia studies. In summary, this study has brought a new perspective to the literature to facilitate the administration of chemotherapeutic drugs with hyperthermia.

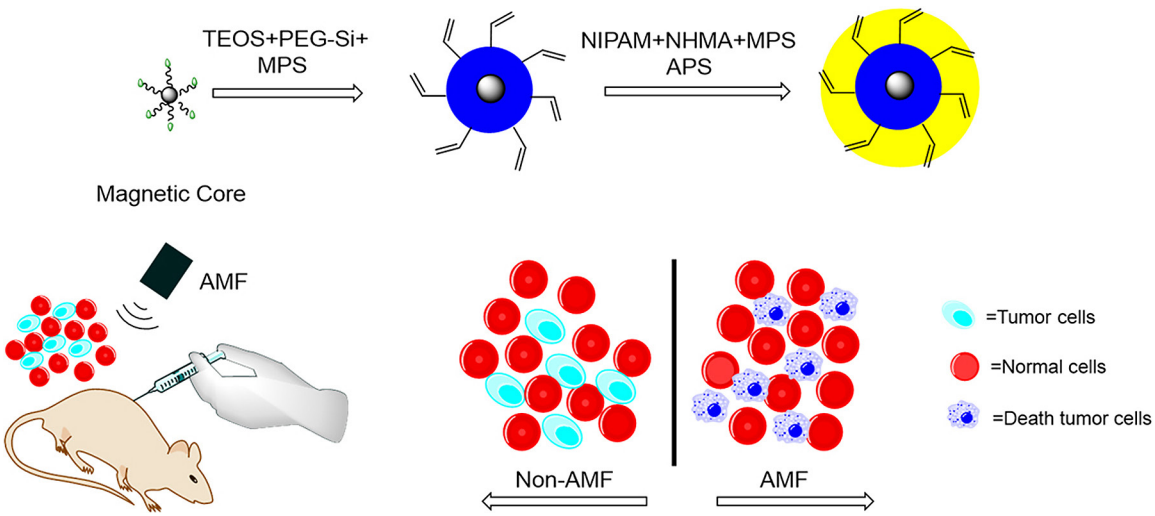

Figure 7. Synthesis of magnetic mesoporosis silica porous nanoparticles and schematic demonstration of drug release applications (Guisasola *et al.*, 2018).

Chen *et al.* encapsulated curcumin into a structure with a magnetic core and coated it with a diblock copolymer, poly(2-methacryloxyethyl phosphorylcholine)-block-poly(serinyl acrylate) (PMPC-b-PserA). $FeCl_3$ was used to form a magnetic core in the structure (Chen *et al.*, 2021). The reason for choosing PMPC as the polymer is due to its similarity to the antifouling structure of the cell membrane. The synthesis process was carried out by addition-fragmentation chain transfer polymerization. Physicochemical characterizations of the synthesized structure were carried out. According to the findings obtained from the hydrodynamic diameter measurement results, the hydrodynamic diameter of the MNPs was determined as 22 nm. Then, turmeric, a hydrophobic polyphenol, was encapsulated. The encapsulation efficiency was determined as 99.6%. However, it was observed that drug release increased in high active ingredient concentrations and acidic pH regions. In addition, *in vivo* experiments showed that cell viability decreased to 34.3% after a 24 h release period. As a result, this nanoplatform developed for effective drug release is extremely important in drug delivery loading efficiency.

Lee *et al.* developed microrobots to release doxorubicin (Lee *et al.*, 2021). This developed microrobot was designed with high doxorubicin loading efficiency, capable of conjugating MNPs with disulfide bonds, and was developed with the helical

structure of a biodegradable PEGDA-based polymer with high biocompatibility. These developed microrobots can move toward the target area under an external stimulus. If the functions of the MNPs in the structure are mentioned, the MNPs separated by external stimuli are recovered by the application of the electromagnetic field, thus ensuring the targeted movement of the microrobot. The fact that the microrobot is on a polymer basis allows it to release the drug by hydrolysis over time. This information has been verified by conducting drug release studies. In addition, it has been confirmed that the microrobot developed by drug release studies can be manipulated with the effect of the electromagnetic field and NIR. Subsequent *in vivo* experiments concluded that microrobot systems containing MNPs and separated and reassembled did not inhibit the growth of normal cells. In addition, it was confirmed by *in vivo* experiments that the drug encapsulated in this structure showed anti-tumor properties. In conclusion, this study is one of the pioneering studies for developing microrobots to realize drug release in cancer treatments.

Mai *et al.* (2022) synthesized iron oxide nanocubes and modified them with catechol furfuryl and PEG. Catechol groups in the structure functioned in the h-strong binding of polymer ligands to iron oxide nanocubes. The PEG groups, on the other hand, minimized the tendency of the iron oxide nanocubes to aggregate and collapse due to their magnetic properties, thus providing good colloidal stability. After this step, fluorescein, a dye type, was bound and doxorubicin was added. According to the findings, the macroscopic temperature decreased in the 1-5 µM range without any change at low nanocube doses. As a result, this magnetic nanocube formulation developed is extremely important for both dose-independent release of drug release and hyperthermia release with the effect of a magnetic field (Mai *et al.*, 2022)

3.2. Enzyme Immobilization

Enzymes are biomolecules that catalyze biological reactions and play an important role in their vital activities. There are major factors that distinguish enzymes from ordinary catalysts. These can be listed as -specific and faster work than other catalysts (Min and Yoo, 2014). There are various factors such as optimum pH, optimum temperature, a certain substrate concentration, etc., at which each enzyme shows maximum activity. However, since enzymes are biomolecules in protein structure, they are not resistant to changing these conditions. Changing the environmental conditions causes the enzymes to denature by disrupting the protein structure. To avoid this situation, enzymes can usually be immobilized on carrier support. The selected carrier matrix can be selected from inorganic, organic, or hybrid structures according to the application condition of the enzyme. The use of MNPs in the field of enzyme immobilization has become increasingly widespread in recent years. The remote controllability of enzymes immobilized on MNPs under a magnetic field, and the ability to trigger enzyme activity have made these materials interesting. In this section, we will discuss the use of polymer-modified MNPs in enzyme immobilization.

MS and Nampoothiri immobilized xylose dehydrogenase on nanoparticles with ferromagnetic properties. (MS and Nampoothiri, 2022). Here the enzyme was obtained by purification from *E. coli.* Xylose dehydrogenase mainly uses NAD^+ and $NADP^+$ to catalyze D-xylose to D-xylonolactone. Subsequently, the reaction product, D-xylonolactone, self-catalyzes to D-xylonolic acid. The immobilization of this enzyme is essential for the food industry. First, ferromagnetic nanoparticles were synthesized and their characterization was completed and functionalized with APTES (Fig. 8). Then, xylosedehydrogenase was immobilized using glutaraldehyde to perform covalent immobilization. According to the findings obtained from the experimental data, the immobilized enzyme preserved its initial activity by 93% even after ten usage cycles, resulting in the formation of 250 mM xylonic acid. Considering this result, it can be said that it is highly advantageous to use this carrier platform to obtain xylonic acid and similar commodity products.

Gebreyohannes *et al.* developed a platform for the degradation of organophosphates (Fig. 9). In this context, polyvinylidene fluoride (PVDF) was preferred as the first hydrophobic porous membrane in their study (Gebreyohannes *et al.*, 2018). The immobilized enzyme is phosphotriesterase-like Lactonase (PLL) purified from *S. solfataricus.* Magnetic nanoparticles were incorporated into the structure after the enzyme was bound to the PVDF membrane via covalent bonding. Enzymes may lose some of their catalytic activity while being immobilized. In this study, magnetic nanoparticles were used to prevent this situation. Enzyme activation can be controlled by inducing magnetic nanoparticles externally with an external magnetic

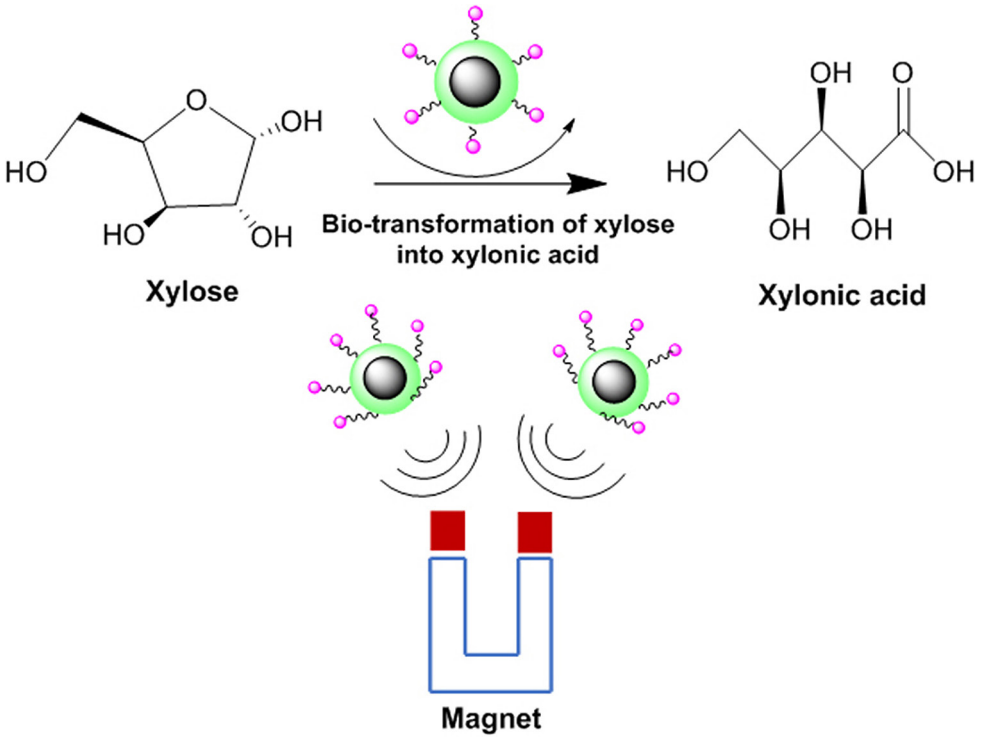

Figure 8. Synthesis of xylanase immobilized ferromagnetic NPs.(MS and Nampoothiri, 2022).

field. After this material was synthesized, the characterization processes were completed. Then, this platform's kinetic properties and immobilization effect were investigated by various experimental procedures. According to the findings obtained from the experimental data, the system using magnetic nanoparticles showed over 90% catalytic performance compared to the non-used system. It was also observed that it increased the reaction rate by approximately 80%. As a result, although the developed platform focuses on the degradation and phosphotriesterase mobilization of organophosphates, it can be developed for immobilizing enzymes used in various commercial applications.

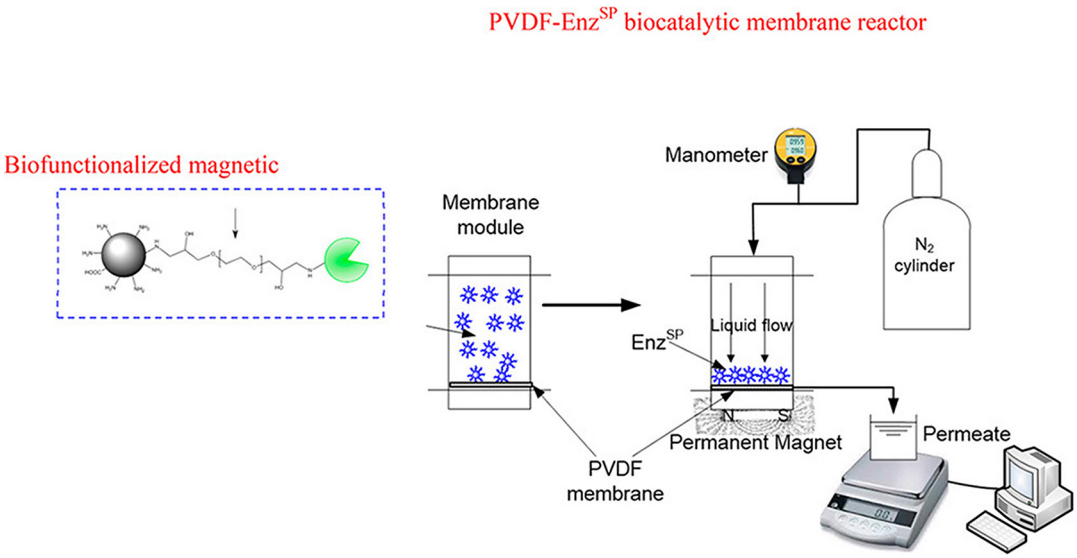

Figure 9. Synthesis and functionalization of magnetic nanoparticles for the degradation of organophosphates (Gebreyohannes *et al.*, 2018).

Shen *et al.* developed a mimic magnetic enzyme carrier matrix with innovative functional properties and immobilized glucose oxidase (GOx). DNA-directed (DDI) technology was used to minimize the loss of activity caused by immobilization just before the immobilization process takes place (Fig. 10.). They also developed a layer consisting of lanthanide metals and nucleotides that protect DDI enzymes in this structure. DNA strands are preferred because of their good physicochemical properties and ability to adjust the appropriate mechanical stiffness. The nano-coating in the structure protected GOx from environmental conditions and prevented it from being denatured. The findings obtained from the experimental data were measured by incubation at 60º for 60 minutes and 120 min. Results were observed to preserve 83% and 64% of initial activity, respectively. Experiments on storage stability show that encapsulated samples kept at 4°C retained 94% of their initial activity even after 45 days. In addition, reusability studies have shown that it retains 81% of its initial activity after 20 cycles of use. In summary, this developed system improved the catalytic activity compared to free enzymes and significantly increased enzyme activation (Shen *et al.*, 2019).

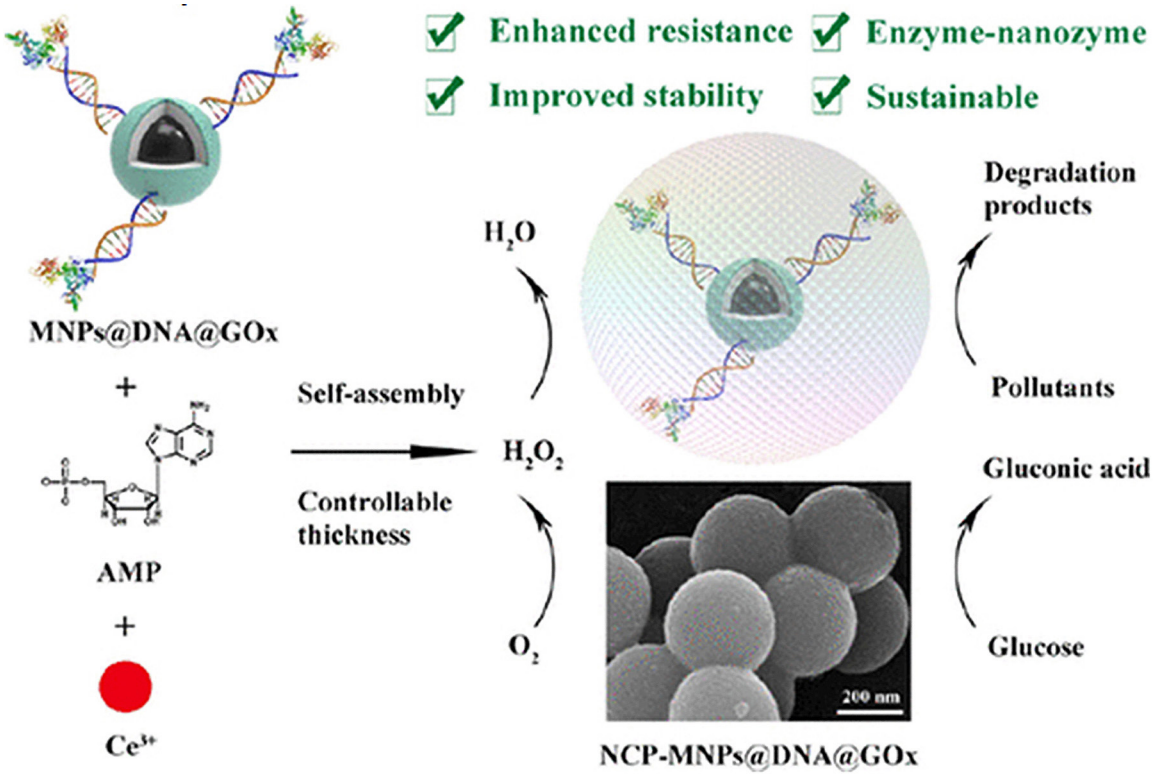

Figure 10. Synthesis of DNA functional magnetic nanoparticles and GOx immobilization (Shen *et al.*, 2019).

2018 Hosseini *et al.* synthesized Fe_3O_4 NPs for cellulase immobilization and imprisoned in an epoxy polymer (Hosseini *et al.*, 2018). The presence of epoxy groups has been used to attach cellulase covalently (Fig. 11). The ionic surface of the epoxy groups increased the interaction of the enzyme and the carrier support, resulting in a high rate of enzyme immobilization. This rate has been reported as 106.1 mg/g. Various physicochemical characterizations analyzed the synthesized Fe_3O_4@Epxy NPs. Reusability experiments were carried out to examine the activity and stability of the enzyme. According to the results obtained from this experiment, the immobilized cellulase retained 60% of its initial activity after six cycles of use. The results show that the carrier support with epoxy/ionic groups is a good choice for enzyme immobilization and has a significant potential for high-scale glucose synthesis.

Figure 11. Synthesis of Fe_3O_4 magnetic nanoparticles and cellulase immobilization (Hosseini *et al.,* 2018).

A recent study by Tang *et al.*, Fe_3O_4 NPs were synthesized and performed lipase immobilization. In this study, unlike standard immobilization studies, the region to be immobilized was determined in advance the immobilization process was performed, and the higher immobilization efficiency was etched (Tang *et al.,* 2022) The immobilization process was carried out covalently. After Fe_3O_4 nanoparticles were synthesized, polyphenols were preferred for surface modification (Fig. 12). The presence of polyphenols in the structure directly affects the immobilization efficiency by providing the active tips required for immobilization. The immobilization method performed in this study showed the advantage of the method by showing 71.3% recovery compared to ordinary immobilization methods. In addition, it showed 92.1% biodiesel efficiency compared to free and ordinary immobilization efficiency. In addition, reusability studies of the lipase immobilized with this system were carried out, and it was observed that 75.3% of its initial activity was preserved. Based on these results, we can say that this system is a suitable catalyst for biodiesel yield, and the reaction specificity is presented in harmony with 3D technology.

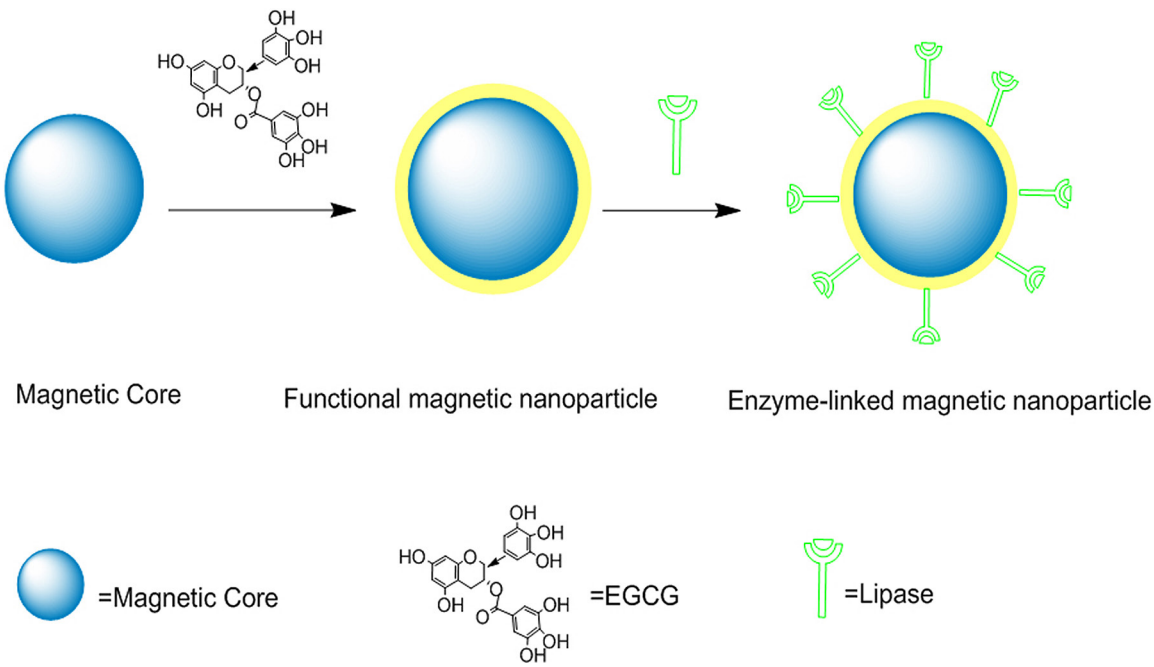

Figure 12. Synthesis of magnetic nanoparticles and realization of lipase immobilization (Tang *et al.,* 2022).

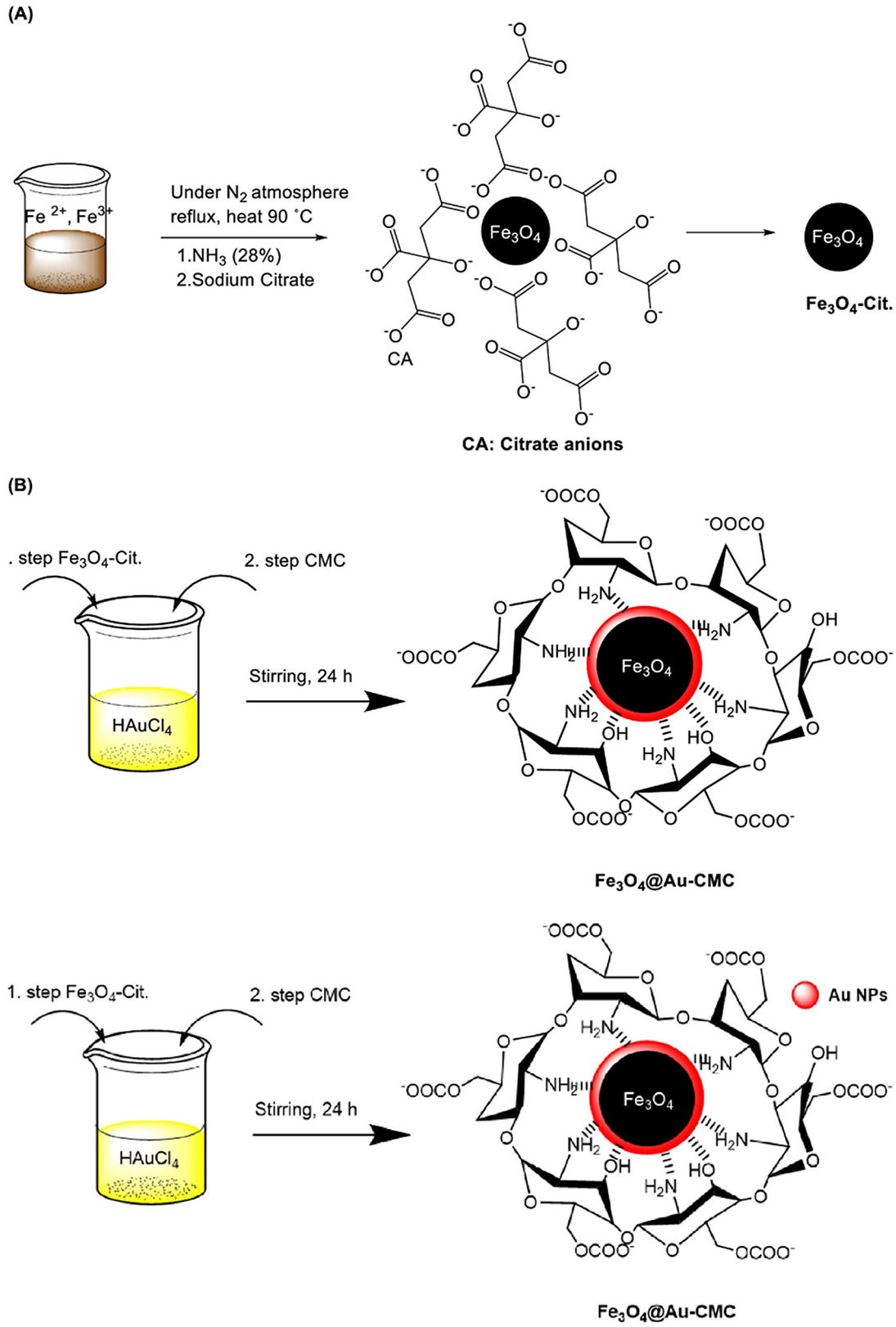

Figure 13. Synthesis scheme of Fe3O4@Au/CMC (Tarhan *et al.*, 2022).

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In our previous study, L-asparaginase (L-ASNase) was immobilized on carboxymethyl chitosan (CMC) included magnetic nanoparticle core (Tarhan *et al.*, 2022). The visual of this experiment is schematized in Fig. 13. The immobilization method between the enzyme and the carrier support was carried out by adsorption. The immobilization efficiency was calculated after various physicochemical characterizations of the developed Fe_3O_4@Au-CMC and Fe_3O_4@Au-CMC-L-ASNase. This value was determined as 68%. However, the optimum temperature value was found to be 50º, while the optimum pH value was determined to be 7. After that, the kinetic parameters were determined. The K_m value indicating the affinity of the enzyme with the substrate was found to be 3.27±0.48 mM, and the V_{max} value indicating the reaction rate was 51.54±0.51. In addition, according to the findings obtained from the reusability studies, it was observed that Fe_3O_4@Au-CMC-L-ASNase preserved 75% of its initial activity. As a result, we can say that this system is highly advantageous for performing enzyme immobilization on magnetic nanoparticles that are functionalized or coated with polymers.

In another previous study, MNPs were synthesized by the co-precipitation method, and L-ASNase immobilization was performed (Dik *et al.*, 2022). After synthesis, magnetic nanoparticles were treated with APTMS to provide amino groups (Fig. 14). Then, 4 of the magnetic nanoparticles were modified with vinyl phenylboronic acid (4-VPBA). As a final step, it is functionalized with PEG to increase its solubility in water. Various physicochemical analyzes were used to characterization of the

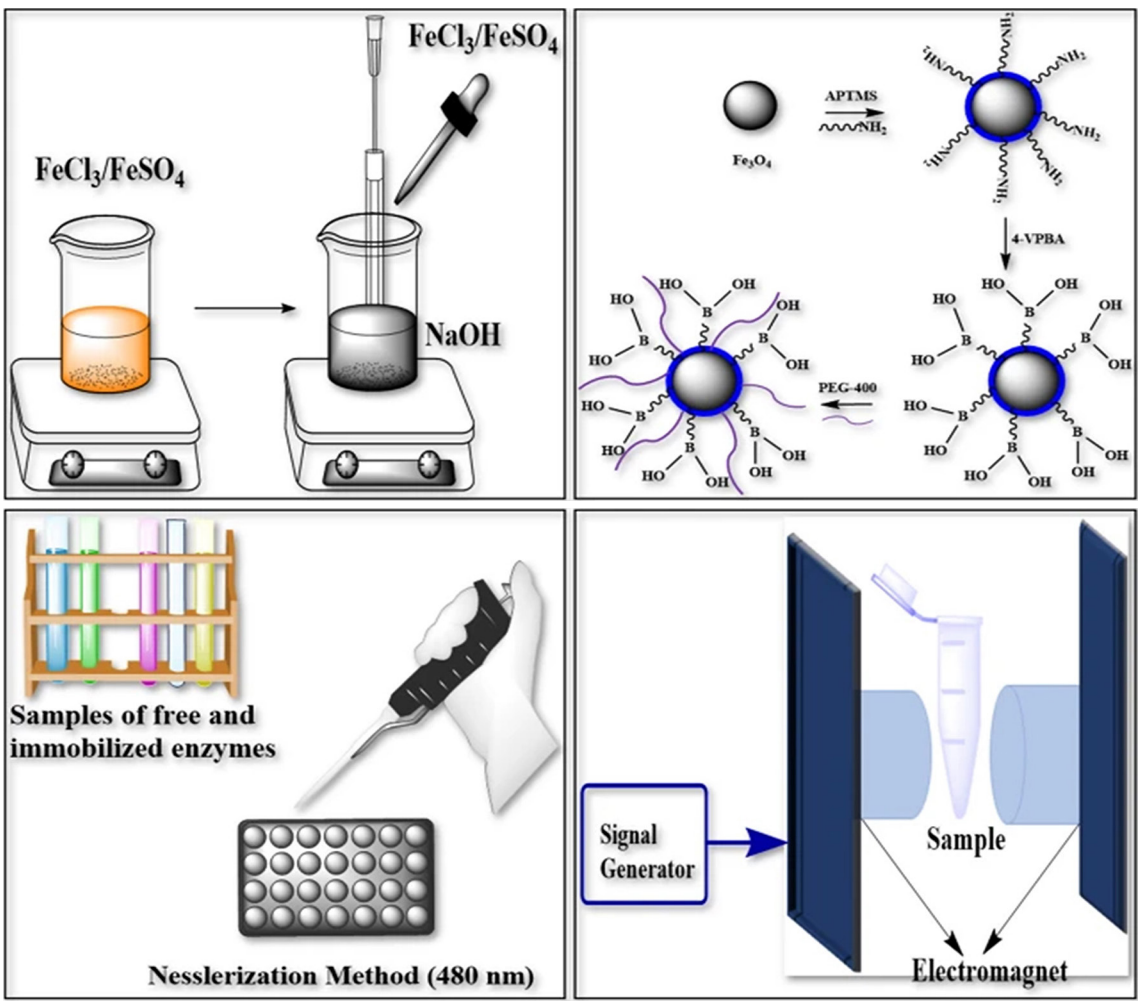

Figure 14. Schematic representation of Fe_3O_4-NH_2-4VPBA-L-ASNase expression, activity measurement and magnetic field application (Dik *et al.*, 2022).

synthesized nanoparticles. According to the findings obtained from the subsequent activity experiments, the free enzyme's optimum pH value was 8.5. In contrast, this value was determined as 7.5 for Fe_3O_4-NH_2-4VPBA-L-ASNase. When the optimum temperature values were examined, it was determined that the optimum temperature value of the free enzyme was 45º, while Fe_3O_4-NH_2-4VPBA-L-ASNase showed maximum activity at 40º. However, reusability studies show that Fe_3O_4-NH_2-4VPBA-L-ASNase retains approximately 54% of its initial activity. Another contribution of this study to the literature is the triggering of enzyme activity with a magnetic field. In this context, magnetic flux and magnetic field scanning were performed, and their activities were measured. According to the findings, 10 Hz and 20 mT increased by 3.2 and 4.3 times, respectively, and reached their maximum. In summary, this study is one of the preliminary studies for the magnetic nanoparticle carrier systems modified with a polymer to be triggered by the magnetic field by immobilizing the enzyme.

3.3. Biosensor Applications

Early diagnosis and treatment of diseases is one of the most important issues that should be emphasized. In recent years, joint studies of medical, science, and engineering fields have been aimed at the early diagnosis of certain diseases, starting with this purpose. For this purpose, it is aimed to develop specific biosensors. Biosensors can be used to diagnose various diseases, from covid 19 to the detection of cancer agents. In addition, the developed biosensors' rapid, high linearity, and high resolution are extremely important for biomedical fields (Nabaei and Heidari, 2018).

For this reason, the development and production of biosensors with an innovative perspective is increasing. Of course, biosensor systems containing magnetic nanoparticles have some advantages over fluorescent-based ones. Some can be listed as follows: i) magnetic biosensors are more stable, ii) background noises originating from fluorescently labeled biosensors are not observed in magnetic-based biosensors, and iii) remote control and regulation can be achieved by applying the magnetic field. However, it is known that the sensitivity of magnetic biosensors is higher than other biosensor systems. This section will discuss the efficacy of biosensor systems containing magnetic nanoparticles.

Jiang *et al.* developed an electrochemical sensor model for the ultra-sensitive detection of Mucin 1 (MUC1). First, 3-D DNA nanomachine signal probes (Nanomachine signal probes) allow CHA to enter the reaction easily. It also combined the

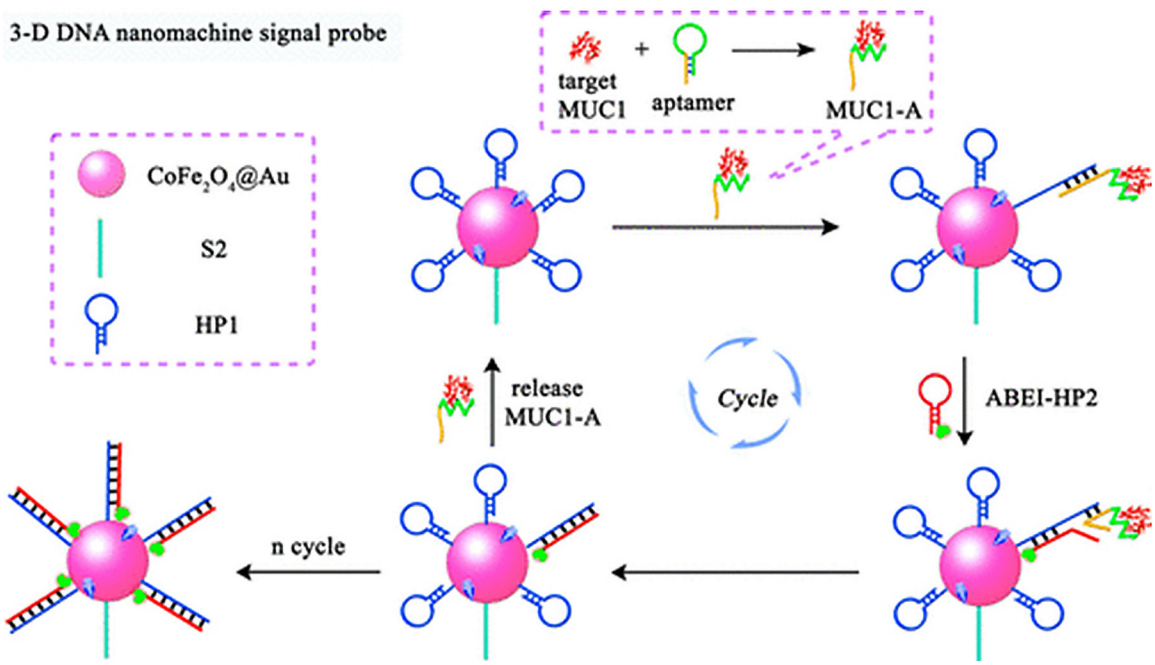

Figure 15. Synthesis of $CoFe_2O_4$@Au nanoparticles and development scheme of DNA nanomachine signal probes (Jiang *et al.*, 2018).

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solution medium, which facilitated the immobilization of the luminophore ABEI, which is in high amounts, on $CoFe_2O_4$. $CoFe_2O_4$ in the structure acts as a carrier of 3-D DNA NSP, which performs the hydrolysis of H_2O_2 to increase the presence of OH^- ions, which are necessary for the realization of the reaction (Fig. 15). However, the reuse of MUC1-aptemaer was distinguished with high sensitivity without any interference effect. According to the findings obtained from the experimental studies, the detection limit of the developed biosensor was determined as 0.62 $g.mL^{-1}$. In summary, we can say that this highly sensitive biosensor is an effective method for determining trace structures to be used in the diagnosis of various diseases (Jiang *et al.*, 2018).

Oropesa-Nuñez *et al.* (2020) investigated biosensor applications by functionalizing magnetic nanoparticles with DNA. Biosensor research was carried out using atomic force microscopy and systems that measure frequency changes (Fig. 16). Within the scope of the study, firstly, magnetic nanoparticles were synthesized and interacted with 4 DNA-helix samples of different concentrations. Morphological characterizations of these structures were performed by atomic force microscopy (AFM) in a liquid medium. The presence of clusters observed with the decrease of the magnetic response of DNA samples with high concentrations, which coincides with the Brownian relaxation motion of magnetic nanoparticles, has been demonstrated. In summary, these hybrid structures' morphological features and magnetic reading variability were presented, and their quantitative and qualitative characteristics were revealed. The study presented a different perspective for sensor applications in a hybrid form of DNA and magnetic nanoparticle structures (Oropesa-Nuñez *et al.*, 2020)

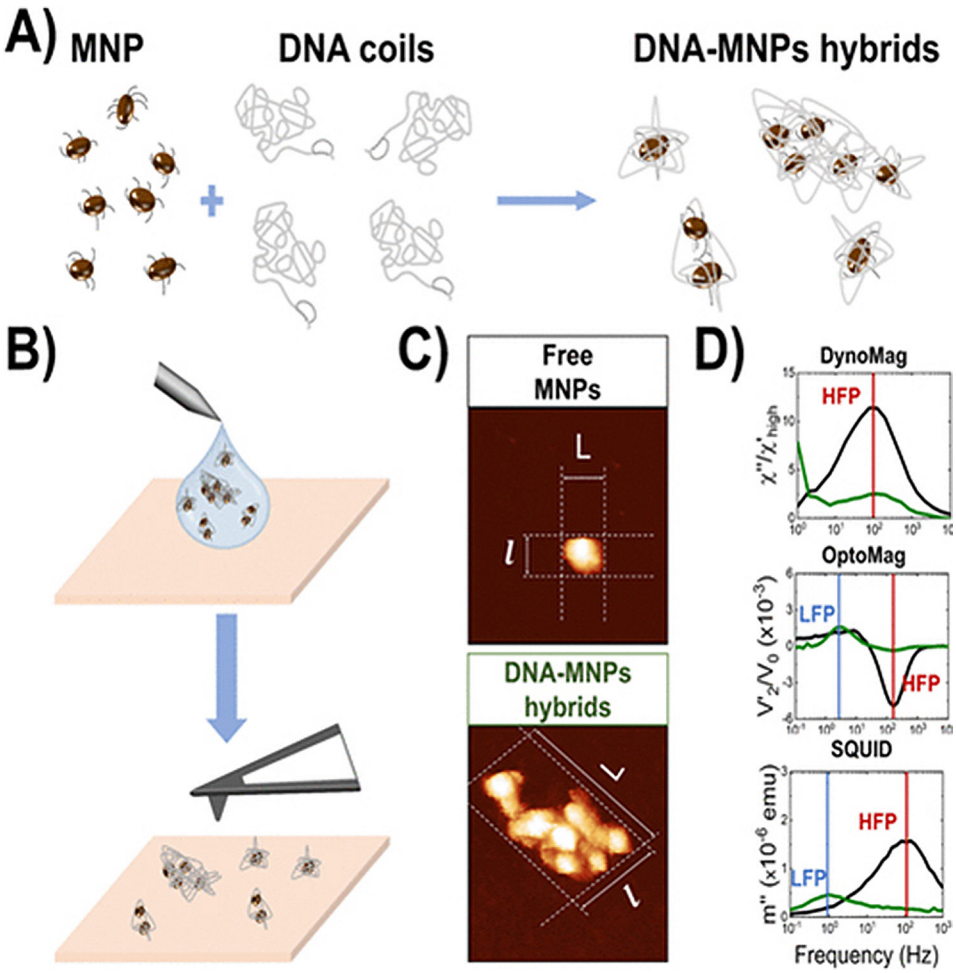

Figure 16. Schematic representation of synthesized magnetic nanoparticles (Oropesa-Nuñez *et al.*, 2020).

Another interesting study developed a biosensor to detect Aryloxyphenoxypropionate (AOPP) herbicides (Ma *et al.*, 2021). For this purpose, AOPP herbicide hydrolase QpeH and Alcohol Oxidase (AOx) were immobilized to the structure. Within the scope of the study, the synthesis of magnetic ZIF-8s was carried out in 3 stages, and OpeH/AOx@mZIF-8 was obtained (Fig. 17). Thanks to the developed system, herbicides can be detected visibly at low concentrations. First, AOPP catalyzes the herbicides with embedded OpeH to form fatty acids and alkaloids in the system. After this reaction, AOx consumes the alcohol in the environment and produces H_2O_2. This developed biosensor is extremely important for low detection limit, high enzyme activity, and storage stability. It has important potential in terms of development in studies for detecting other microorganisms.

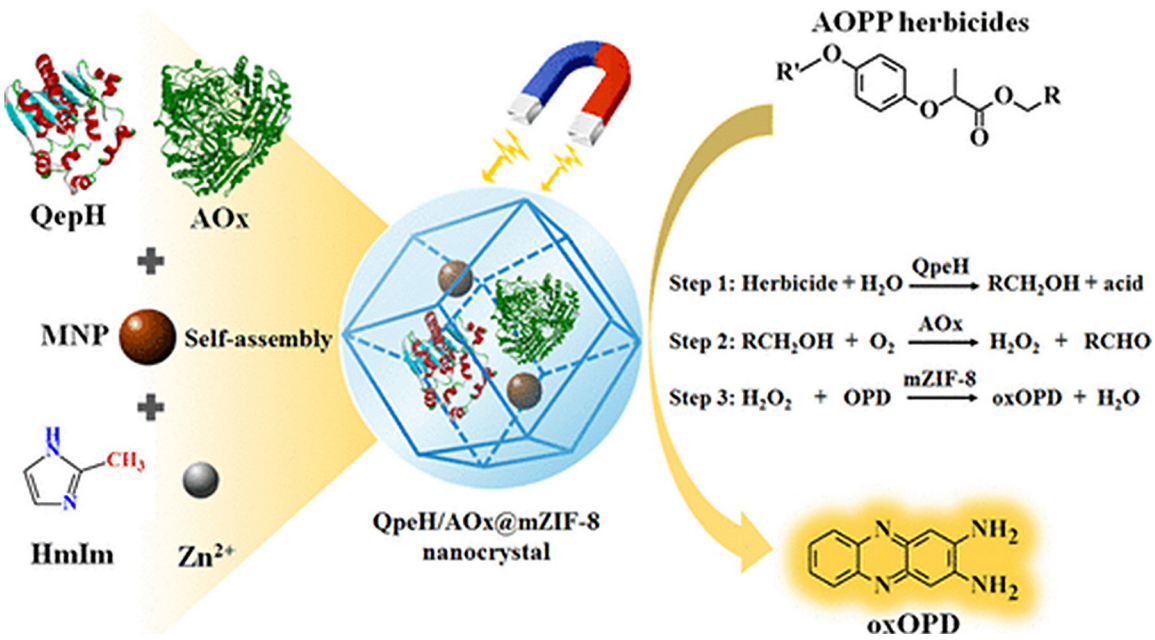

Figure 17. Synthesis of magnetic ZIF-8s and their use as sensors for detecting microorganisms (Ma, *et al.*, 2021).

3.4. MRI Imaging

In recent years, magnetic nanoparticles have been widely used in magnetic resonance imaging (MRI) due to the effective increase in relaxation. The use of magnetic nanoparticles as magnetic resonance imaging probes has been the subject of different studies due to their superior contrast enhancement abilities (Katti *et al.*, 2011). Image acquisition by MR, which has many different applications, from tumor visualization to cardiac mapping, is due to the proton relaxation rate produced by a contrast agent in the presence of EMF. Its basic principle is based on detecting the magnetic moments of protons aligned with the field direction. It causes rotation when a suitable radio frequency is applied (in 'resonance' with protons) and absorbed by the latter. When the EMF is removed, the proton relaxes. During such a relaxation process, the receiving coils generate and detect a weak radio frequency (Degen *et al.*, 2009), which allows the image to be generated by the software. Identifying key factors influencing MR imaging *in vitro* (T2) transverse relaxation and *in vivo* visualization is critical for the design of magnetic nanoparticles. Using a high-temperature separation method in the organic phase, magnetic nanoparticles exhibit good qualities such as size distribution, crystalline structure, and magnetic properties, but their hydrophobic nature limits their biomedical applications. To overcome this problem, coating the surface of magnetic nanoparticles with polymers is a suitable method so that after polymerization, generally water-soluble magnetic nanospheres are formed (Liang *et al.*, 2000). A higher cluster density of magnetic nanocrystals, in turn, is beneficial for the production of sensitive T2 materials. A better understanding of magnetic nanoparticles will aid in designing sensitive MRI T2 contrast agents for

use in various biomedical applications. The development of magnetic nanoparticle-based probes with high cell-drug labeling efficiency, specific targeting, or environmentally sensitive properties (such as T1-T2 switchable contrast agents) is an important area for further development. It may provide opportunities for solving pre-clinical problems in the future (Weishaupt *et al.*, 2006).

Concerning the synthesis method, magnetic nanoparticles show superior properties such as obtaining controlled sizes, crystalline properties, and being triggered by a magnetic field. However, to avoid some disadvantages due to their hydrophobic nature, they must be coated with a suitable polymer. Hu *et al.* In this study, magnetic nanoparticles were synthesized and functionalized with oligonucleotides. The main principle of my work is to detect the presence of Hg^{2+} in the medium based on the specific and strong interaction between mercury ion and thymine-thymine (T-T) mismatch in DNA duplexes, using the oligonucleotide functionalized magnetic nanoparticle as magnetic capture probe and MRS signal probe, respectively. The stages of the study are shown in Fig. 18. According to the findings, the concentration-dependent MRS mode showed a wider detection range of Hg^{2+} metal ion in various water samples and serum (Hu *et al.*, 2020).

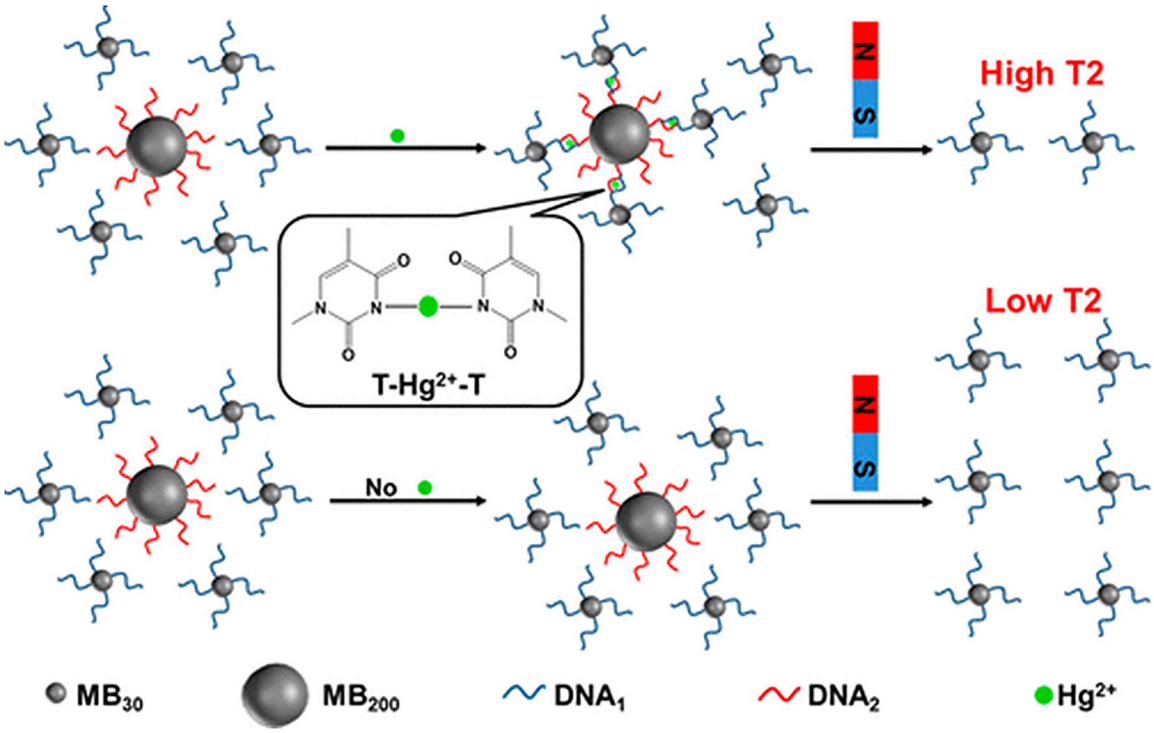

Figure 18. Schematic representation of the system developed for detecting Hg^{2+} ions (Hu *et al.*, 2020).

According to Mekseriwattana *et al.* synthesized superparamagnetic iron oxides and functionalized with riboflavin (Rf)-citrate ligand (Fig. 19.). This realized system has been studied in the treatment of breast cancer as T2 contrast agents for magnetic resonance imaging (Mekseriwattana *et al.*, 2023). Fatal bovine serum was used to examine the interactions of riboflavin-functionalized magnetic nanoparticles with proteins. All materials synthesized in the study were characterized by various analyzes. Results from proteomic analysis were determined by comparison with FBS-derived coronas to understand differences in protein corona formation from various serum sources. The findings indicated that the results between the FBS and HS groups showed similar characteristics. However, interactions of some specific homologous proteins have been observed. It was determined that the citrate coated magnetic nanoparticles showed higher binding rate. The result can be explained by molecular dynamics simulation where the orientation of the Rf ligand does not favor binding with RCP.

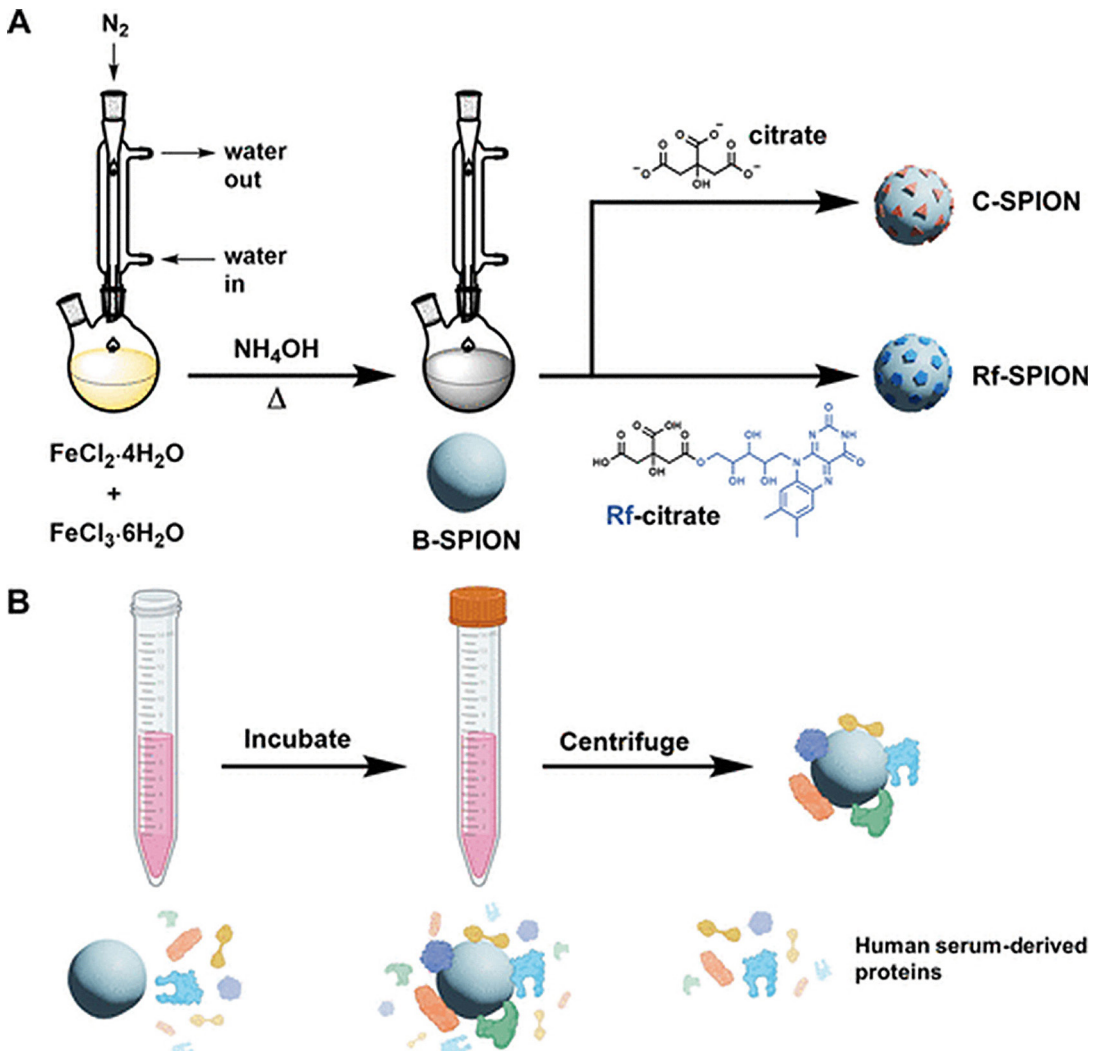

Figure 19. Experimental scheme (A) Synthesis of superparamagnetic Iron oxides (B) Protein corona formed (Mekseriwattana *et al.*, 2023).

Demin *et al.* synthesized iron oxide nanoparticles and modified their surfaces with N-(phosphonomethyl) iminodiacetic acid (PMIDA) (Demin *et al.*, 2018). These developed nanoparticles are designed for magnetic resonance imaging (Fig. 20.). After the synthesis and modification process, a series of experimental procedures were followed to observe how much the amount of PMIDA added and other environmental factors affected the degree of immobilization. It was observed that the most suitable environmental conditions for immobilization were obtained with the reaction of 40° for 3.5 hours. The obtained materials were characterized by FTIR, SEM, XRD, and EDX analyses. It has been observed that these functionalized nanoparticles have good colloidal stability and high magnetization. The calculated relaxations r2 and r1 were determined as 341 and 102 $mmol^{-1}s^{-1}$, respectively. In addition, in this study, magnetic nanoparticles functionalized with PMIDA were used as a T2 contrast agent in *in vivo* liver studies.

3.5. Hyperthermia

Hyperthermia is a method used to destroy or treat tumor cells by increasing the temperature of the cells. This treatment method can be developed by using different procedures and various drugs in combination. The energy required for heating used to treat hyperthermia can be obtained from different sources (Behrouzkia *et al.*, 2016). These sources include microwaves, radio waves, ultrasound, and magnetic

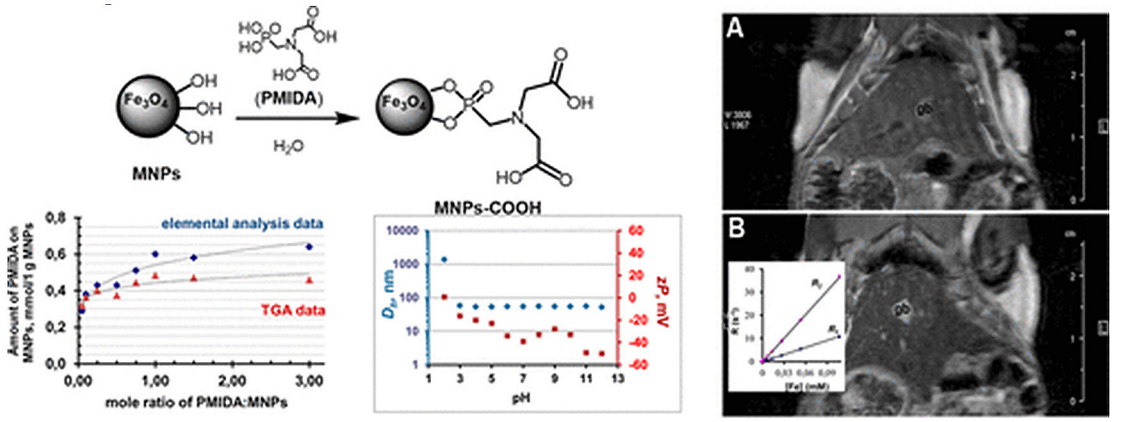

Figure 20. Synthesis of PMIDA functional magnetic nanoparticles and their use in imaging (Demin *et al.*, 2018).

field. The choice of energy source can be changed according to the type of cancer and its location. Naturally, the heating rate will change with the change of the energy source. With the help of magnetic field and magnetic nanoparticles, hyperthermia treatment is one of the potentially most important biomedical applications currently known. Recent studies confirm that this practical method of localized remote heating of body tissue, with or without radiotherapy or chemotherapy, has significant potential in cancer treatment. This section will discuss some studies carried out within the scope of magnetic hyperthermia treatment (Ortega and Pankhurst, 2013).

Duraisamy *et al.* synthesized nickel and iron iron-supported fluoropatite nanoparticles with magnetic properties. The synthesis scheme of the study is shown in Fig. 21. After the synthesis process, the structural and magnetic properties were characterized by various analyzes, such as XRD and VSM. As a result of the analysis, phases of both magnetite and fluoroapatite were determined. The detected material reached a temperature of about 43°C in 2.67 min under conditions mimicking a tumor's presence. In addition, the specific loss power (SLP) was predicted to be 898 W/g (Ni+Fe). This result was found to be sufficient to initiate permanent cell

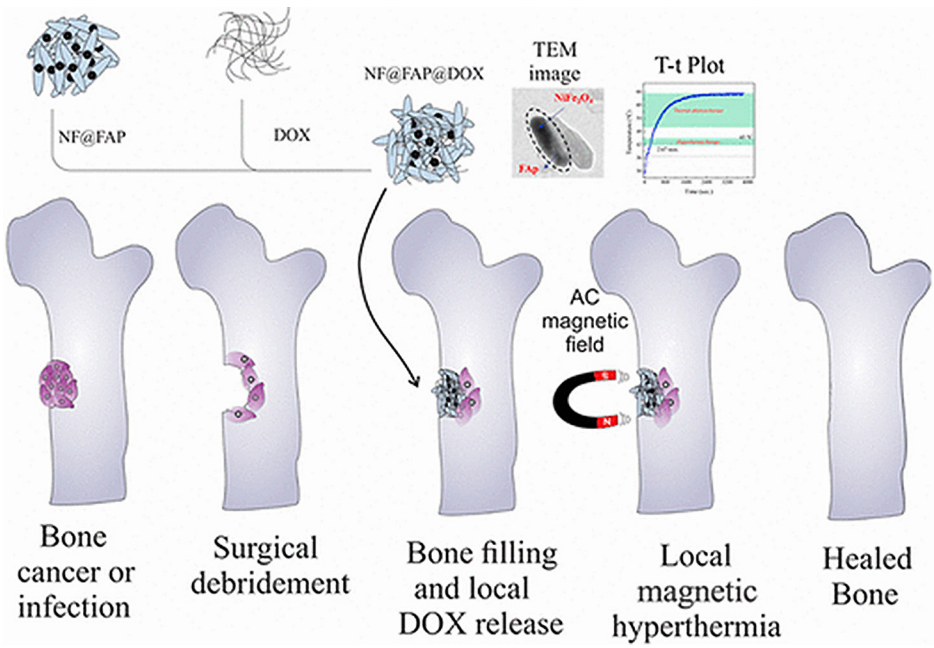

Figure 21. Synthesis and applications of nickel and ferrite-supported fluoroapatite nanoparticles (Duraisamy *et al.*, 2022).

apoptosis. In addition, drug release tests were carried out under *in vitro* conditions under two different ambient conditions, pH 5 and pH 7.4. According to the findings, a 49.8% release in an acidic medium and 11.6% in neutral medium was revealed after 11 days. Finally, it was observed that the obtained material exhibited antibacterial activity against S. aureus (Duraisamy *et al.*, 2022).

In thermal therapy, it is very important to synthesize magnetic nanoparticles that can generate heat during therapy, observe the course of treatment and have functional properties. Vinicius-Araujo *et al.* (2021) developed a nanocarrier system that both realizes hyperthermia using magnetic nanoparticles and incorporates photothermal therapy (Fig. 22.). In addition, this nanocarrier system shows luminescent nanothermometry properties. According to the findings obtained from the study, the photothermal conversion efficiency increased from 17% to 24% as the amount of Nd^{3+} in the silica-coated nanoparticles was increased under low laser power conditions. Negative effects were observed in the conditions where the laser power was increased. This situation has been prevented by changing the outer shell thickness, which preserves the PCE value. In addition, photoexcitation was performed at 808 nm, allowing magnetic hyperthermia and photothermal therapy to synergize. Due to the hemolytic activity of the silica coating on the nanoparticle surface on non-red blood cells, it was observed that coating the surface of the nanocarrier with bovine serum albumin significantly reduced the hemolytic activity (Vinicius-Araujo *et al.*, 2021).

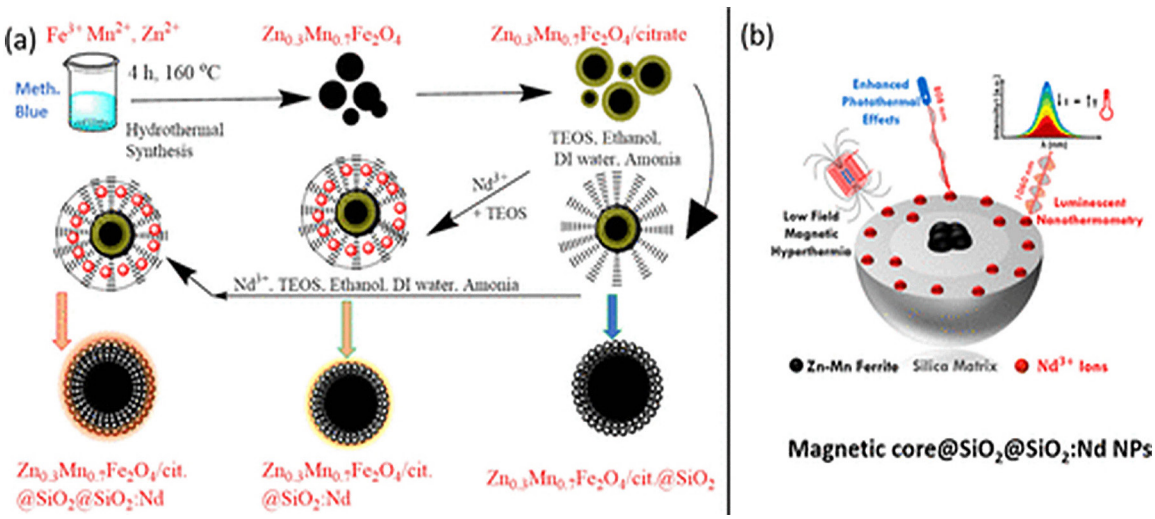

Figure 22. Use of silica coated magnetic nanoparticles in photothermal and hyperthermia treatment (Vinicius-Araujo *et al.*, 2021).

Surface coatings are very important for the heating effects of the material. Fernández-Afonso *et al.* (2022) coated the surface of magnetic nanoparticles with two different materials, PMAO (polymaleic anhydride-alt-1-octadecene) and DMSA (dimercaptosuccinic acid) (Fig. 23). The size of the obtained nanoparticles was found to be around 13 nm. Afterwards, their degradation was investigated in an environment mimicking lysosome conditions. Changes in the physical properties of the nanoparticles were followed for 24 days. It has been observed that nanoparticles coated with DMSA degrade faster than PMAO-coated nanoparticles. In addition, the heating properties of the samples exposed to both alternating magnetic field and NIR light, how their heating capacity was affected, and their structural and morphological properties were also evaluated. It has been reported that changes in magnetic hyperthermia measurements during the decomposition process are more pronounced than photothermal measurements. This study will contribute to developing nanocarrier formulations for treating magnetic hyperthermia (Fernández-Afonso *et al.*, 2022).

Zufelato *et al.* In their study, they synthesized Mn-Ferrite-based nanoparticles with different diameters and investigated the magnetic hyperthermia properties. The stages of the study are shown in Fig. 24. After the synthesis process was completed, the structural and morphological features were

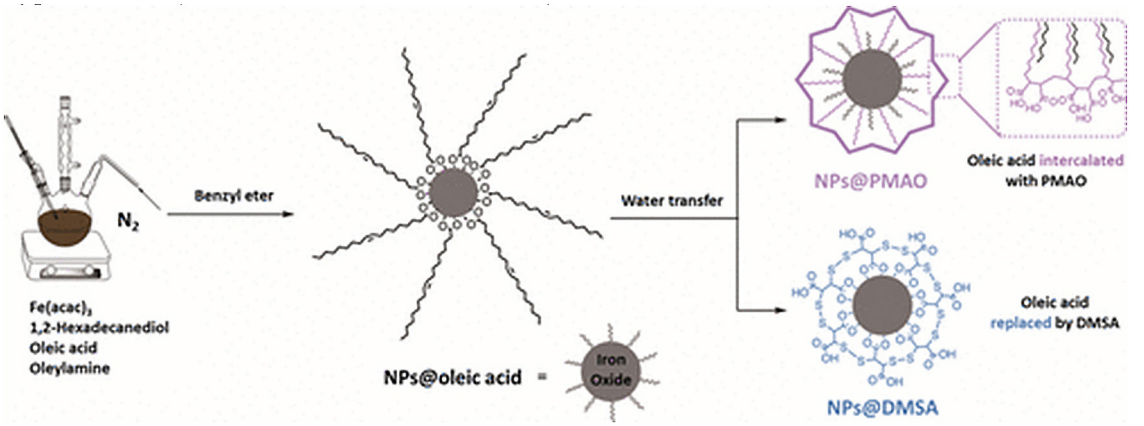

Figure 23. Schematic of synthesis and coating of magnetic nanoparticles (Fernández-Afonso *et al.*, 2022).

characterized by various analyzes (Zufelato *et al.*, 2022). The surface coating is of great importance on the fact that Mn-Ferrite-based nanoparticles have different dirodynamic diameters. The BSA coating was realized by changing the conditions, and different hydrodynamic diameters were obtained. It is thought that this study is a practical tool for understanding dynamic regime diagrams and the synthesis and design of magnetic nanostructures, which are of great importance in magnetic hyperthermia.

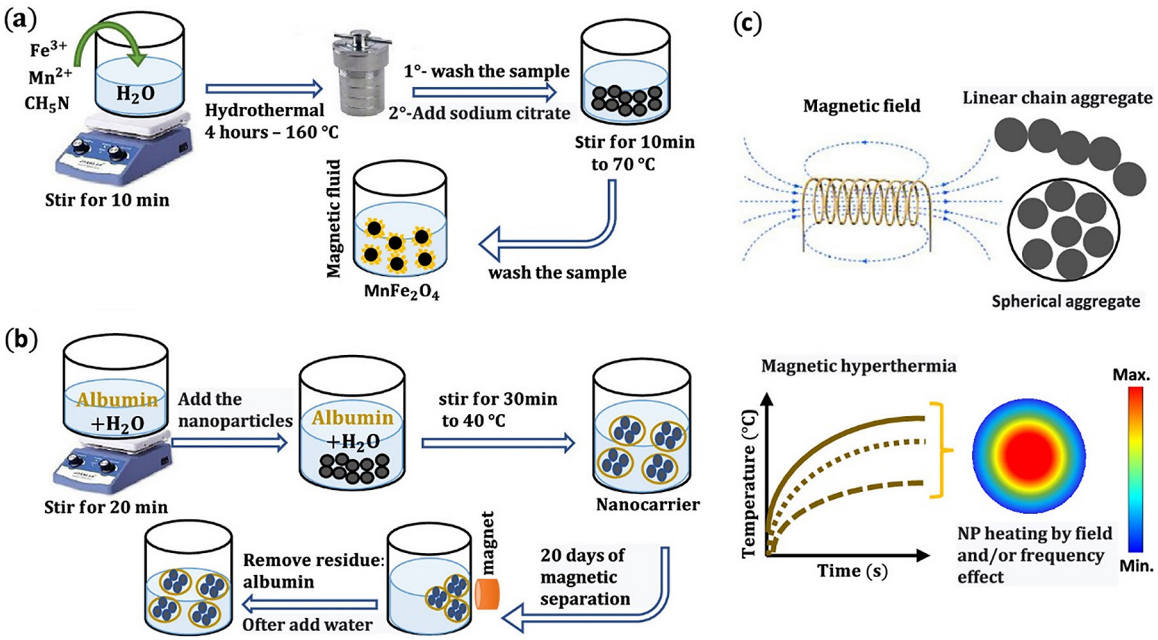

Figure 24. (a,b) Synthesis of Mn-ferrite-based magnetic fluids and BSA-coated Mn-ferrite nanoparticles (c) Investigation of hyperthermia with arrangements performed under different conditions (Zufelato *et al.*, 2022).

4. CONCLUSIONS AND FUTURE OUTLOOK

MNPs are being investigated by many fields due to their low particle size, a wide range of synthesis methods, and magnetic nature. This review emphasizes some applications of magnetic nanoparticles in biomedical fields. Magnetic nanoparticles are widely preferred in biomedical applications such as drug release, enzyme immobilization, and

biosensors. In drug release studies performed with magnetic nanoparticles, the drug can be targeted to the desired area without damaging other tissues and organs, thanks to magnetic nanoparticles. In addition, it is known that both drug release and hyperthermia effects are observed thanks to magnetic nanoparticles. In enzyme immobilization, many enzymes can be immobilized to magnetic nanoparticles. This is extremely important in terms of both the industrial and biomedical fields. Studies on the immobilization of enzyme-drug formulations used in treating some diseases to magnetic nanoparticles are available in the literature. In addition, one of the uses of magnetic nanoparticles in enzyme immobilization is to induce activity decreases during immobilization by applying an external magnetic field. Preferring magnetic nanoparticles in biosensor applications is very important for developing high-sensitivity sensors. Although drug release, enzyme immobilization, and biosensor applications are included in this article, the applications of MNPs are not limited to these. The existing applications of MNPs in tissue engineering and their use as MRI imaging agents are also known. We think this article will shed light on the use of magnetic nanoparticles in biomedical fields and contribute to developing new formulations for this field.

Conflicts of interest

There are no conflicts to declare.

Funding

The authors did not receive funding from any organization for this paper. ♦

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List of Abbreviations

Nanoparticles (NPs); Magnetic Nanoparticles (MNPs); Magnetic Resonance Imaging (MRI); Paclitaxel (PCX); Cold Atmospheric Plasma (CAP); Letrozole (let-7a); Doxorubicin (Dox); Poly(2-methacryloxyethyl phosphorylcholine) (PMPC); Poly(2-methacryloxyethyl phosphorylcholine)-block-poly(serinyl acrylate) (PMPC-b-PserA); Polyethylenglycol (PEG); Near infrared Light (NIR); Aminopropyltriethoxysilane (APTES); Polyvinylidene Fluoride (PVDF); Phosphotriesterase-Like Lactonase (PLL); Glucose Oxidase (GOx); DNA-Directed (DDI); Epoxy (Epxy); L-asparaginase (L-ASNase); Carboxymethyl Chitosan (CMC); 3-Aminopropyltrimethoxysilane (APTMS); 4-Vinyl Phenylboronic Acid (4-VPBA); Mucin 1 (MUC1); N-(aminobutyl)-N-(ethylisoluminol) (ABEI); Atomic Force Microscopy (AFM); Alcohol Oxidase (AOx); Aryloxyphenoxypropionate (AOPP); Riboflavin (Rf); Fetal Bovin Serum (FBS); Human Serum (HS); N-(phosphonomethyl) iminodiacetic acid (PMIDA); Polymaleic anhydride-alt-1-octadecene (PMAO); Dimercaptosuccinic acid (DMSA).

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